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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,720	12/01/2000	Steven K. H. Foung	2002850-0009	5311

7590 05/16/2003

C. Hunter Baker, M.D., Ph.D.
Choate, Hall & Stewart
53 State Street
Exchange Place
Boston, MA 02109

EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	18

DATE MAILED: 05/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/728,720	FOUNG ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-23,25-32,67,70,92,93 and 95-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-23,25-32,67,70,92,93 and 95-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1, 4-13, 25-27, 30, 32, and 92-100 were amended, claims 3, 66, and 94 were canceled, and new claims 101-105 were added in Paper No. 17 filed 10 February 2003. Claims 1, 4-23, 25-32, 67, 70, 92, 93 and 95-105 are pending and under examination.

Rejections withdrawn

The rejection of claims 12, 13, 95, 96 and 97 under 35 U.S.C. 112, first paragraph, as requiring a biological deposit is withdrawn in view of Applicant's remarks at page 11-13, the statement from Dr. Foung, the assurances provided at page 12, and the amendment to the specification at page 24.

The rejection of claims 93 and 94 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the combination of the antibodies CBH-7 and CBH 4-G, wherein the binding of one antibody to a conformational epitope results in increased binding of the other antibody to a second conformational epitope, does not reasonably provide enablement for any and all combinations of antibodies wherein the combination results in increased binding of the antibodies to one or more conformational HCV E2 epitopes, is withdrawn in view of Applicant's amendment to claim 93 and cancellation of claim 94, and the remarks at pages 15-18 of Paper No. 17. The rejection is not applied to new claims 103-105 for the same reasons.

The rejection of claims 1, 15-19, 21, 22, 25, 26, 28 and 29 over Mondelli et al. is withdrawn in view of Applicant's amendment to claim 1 and remarks at pages 21-22 of Paper No. 17.

The rejection of claims 1, 3, 15, 18, 19, 20, 25, 28 and 29 over Deleersnyder et al. is withdrawn in view of Applicant's amendment to claims 1 and 3 and remarks at page 22 of Paper No. 17.

The rejection of claims 1, 3, 15-19, 21, 22, 25, 26, 28, 29, 92 and 98 over Habersetzer et al. is withdrawn in view of Applicant's amendment to claims 1, 3, and 92 and remarks at pages 23-24 of Paper No. 17.

The rejection of claims 8-13 over Da Silva Cardoso et al. or Burioni et al. is withdrawn in view of Applicant's arguments at pages 25-28 of Paper No. 17, which were considered and found persuasive.

The rejection of claims 8-13 over Deleersnyder et al. or Habersetzer et al. is withdrawn in view of Applicant's arguments at pages 28-29 of Paper No. 17, which were considered and found persuasive.

New objection

The amendment filed 10 February 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The material added at page 6, line 14, is deemed to contain new matter in the second sentence: "The dissociation constants for these antibodies for their epitopes ranges from less than 10^{-7} M to less than 10^{-8} M to less than 10^{-9} M."

Although original claims were drawn to monoclonal antibodies with specific values for binding constants, no support could be located for a range of dissociation constants as appears in the material cited above.

Applicant is required to cancel the new matter in the reply to this Office Action.

New rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 67, 70, and 98-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite in reciting "the step of administering the antibody comprises administering more than one different antibody." It is not clear whether the additional antibody or antibodies must also be an antibody within the scope of claim 1, or whether it or they can be any "different" antibody.

Claims 67 and 70 are indefinite since each claim depends directly or ultimately from canceled claim 66.

Claims 98, 99, and 100 are indefinite since each claim depends from canceled claim 94.

Rejections maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 4-7 are drawn to an antibody directed to a conformational epitope of a protein of hepatitis C virus wherein the dissociation constant, K_D, of the antibody for its epitope has specific values ranging from "less than 10^{-7} M" to "less than 10^{-10} M." While an original claim may be taken to provide written description, the specification does not appear to teach or describe the production and/or selection of antibodies to conformational epitopes of hepatitis C virus with particular values for binding constants, or characterized according to their binding constants for their epitopes, such that one would recognize that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has pointed out the amendment to the specification to provide support for claims 4-7 which were present in the originally filed application. The amendment to the specification is not sufficient, however, and is objected to as containing new matter with respect to ranges of values, as discussed above. It still is not apparent where antibodies with K_D 's with these values were provided for in the specification as filed.

Claims 29, 30-32, 67, 70, and 98-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for reasons of

record in rejecting claims 29, 30-32, 66, 67, 70, and 98-100 in the previous Office action.

Applicant has argued at page 13-15 that Pileri et al. (Science 282:938-941, 1998), a copy of which was provided, show that the *in vitro* NOB assay can be a reliable measure of *in vivo* neutralization activity of antibodies, that Pileri et al. showed that antibodies from sera of chimpanzees vaccinated with E1 and E2 envelope proteins inhibited binding of HCV to CD81 in an NOB assay and that anti-E2 antibodies that neutralize HCV infection *in vivo* can inhibit the binding of HCV to CD81 *in vitro,* supporting the idea that CD81-E2 interaction is relevant to infection; that the present invention correlates *in vitro* NOB activity to potential neutralizing effects *in vivo;* that the NOB assay can predict the *in vivo* neutralizing activity of antibodies, although they are not absolute, since, e.g., Ishi et al. (Hepatology 28(4), 1998, Abstract), a copy of which was provided, found that NOB activity was found in only 2 of 5 patients recovered from acute HCV; that other assays might need to be used and such assays are known in the art, e.g., the administration of candidate antibodies to chimpanzees to test for protection from HCV; that NOB assay can be used to identify antibodies that may be further screened in *in vivo* studies.

These arguments have been considered but not found persuasive. Neither the arguments presented nor the references cited are commensurate in scope with the claims. None of the references concern monoclonal antibodies, but rather test the NOB by polyclonal antibodies that bind to multiple epitopes. Further, as Applicant has aptly pointed out, the NOB assay can be used to identify antibodies that may be further

screened in *in vivo* studies. The correlation between NOB activity and true virus neutralization activity remains to be proven. The references cited tend to show that the state of the art at the time the invention was made supports the lack of predictability in using *in vitro* neutralization of binding assays to correlate with likelihood of success in treating using anti-HCV E2 antibodies in general, and do not provide any evidence with respect to the use of monoclonal antibodies as claimed in treatment. The rejection is maintained.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-23, 25-29, 92-98 and 101-105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 and 59 of copending Application No. 09/430489 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to antibodies that are either the same

as, or have the same binding specificity as, the antibodies of claims 3-5 and 59 of Application No. 09/430489 and thus would have been obvious over those antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has indicated that no response to the provisional rejection is being provided.

The rejection is maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 14, 15, 22, 23, 25, 26, 28, 29, 92, 98, and 101 are rejected under 35 U.S.C. 102(b) as anticipated by WO 97/40167, Persson et al., published 10/30/97, of record, for reasons of record. Persson et al. disclose recombinant human monoclonal antibodies specific for conformational HCV E2 epitopes that have Kd's of as little as 6 nM, i.e., less than 10^{-8} M (see, e.g., Table III).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-13 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Persson et al. for reasons of record. The antibodies of Persson et al. reasonably appear to be the same as, or only slightly different from, the claimed antibodies since they were obtained from HCV infected individuals, they were selected in the same manner, they bind to conformational epitopes on the HCV E2 protein, and they give the same or similar results in neutralization of binding assays; thus, in the absence of factual evidence to the contrary, they reasonably appear to be the same as or only slightly different from the antibodies of claims 8-13.

With respect to the rejections over Persson et al., Applicant has argued that Persson's antibodies were not obtained from a hybridoma, that the instant antibodies were generated against an *in vivo* infection, and that Persson's antibodies were screened against recombinant antigens that may have different epitope binding profiles than native HCV virions.

These arguments have been considered but not found persuasive as they rely on limitations not found in the claims, i.e., the rejected claims do not require hybridomas. Further, Persson's antibodies came from an HCV infected donor, and they behave the same way in neutralization assays as Applicant's antibodies. Applicant has provided neither persuasive argument nor factual evidence that Applicant's antibodies as claimed are structurally or functionally different from Persson's antibodies.

The rejections over Persson are maintained.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US patent 6,538,114 to Persson et al., issued March 25, 2003, cited on PTO 892, attached, discloses human monoclonal antibodies to HCV E2 that are specific for epitopes on more than one HCV genotype.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
May 15, 2003